REMARKS

An Information Disclosure Statement (IDS) and a Request for Continued Examination (RCE) are submitted herewith. Applicant requests that the present Response be entered and that the references listed in the IDS be considered. Applicant has cancelled claims 4, 6, 9, and 35, amended claims 1, 32, 43, and 45, and added new claims 47-49. Claims 1-3, 5, 7-8, 10-19, 32-34, and 36-49 are presented for examination. Pursuant to a restriction requirement, claims 41 and 42 have been withdrawn. Support for the claim amendments and new claims is found in the specification as filed, e.g., at paragraphs [0009], [0011], [0017], [0052], and [0055] of the published application (US 2004/0259832). No new matter has been added.

Applicant received a Notice of Panel Decision mailed on October 14, 2008 ("Notice") in response to a Pre-Appeal Brief Request for Review and a Notice of Appeal filed September 12, 2008. The applicant elects to file the present Response to the Office Action with the enclosed RCE and IDS.

Claim Rejections

35 U.S.C. §112, Second Paragraph

Claims 1-19, and 32-40 are rejected as allegedly being indefinite for the recitation of the term "analog" (Office Action at page 2). Applicant respectfully disagrees. "Claims and disclosures are not to be evaluated in a vacuum. If elements of an invention are well known in the art, the applicant does not have to provide a disclosure that describes those elements." See MPEP 2106. In this case, applicant submits that the term "analog" occurs in the context of claims reciting "an antiherpes substance that inhibits viral DNA replication comprising… a nucleoside analog" (*See, e.g.,* independent claims 1, and 32). The metes and bounds of the recitation of "analogs" that are "an antiherpes substance that inhibits viral DNA replication" constitutes a class of molecules that was well-understood by those of ordinary skill working in the field of herpes infections as of the filing date of the instant application. For example, applicant has previously submitted, and incorporates herein by reference, excerpts from an NIAID Chemical Database (of the National Institutes of Health) that describes "nucleoside

analogs," such as AZT, 3TC, ddI, ddC, D4T and abacavir succinate; a GlaxoSmithKline datasheet for ZOVIRAX® (acyclovir), describing acyclovir as "a synthetic nucleoside analogue," and a paper describing the rational design of antiviral drugs, such as "nucleoside analogs" and "pyrophosphate analogs." Since a person of ordinary skill in the art would readily have understood the term "analogs" in the context of the claimed recitation of "an antiherpes substance that inhibits viral DNA replication comprising… a nucleoside analog," the term "analog" is definite. As such, applicant respectfully requests that the rejection be withdrawn.

35 U.S.C. §112, First Paragraph

Claims 1-19, 32-40, and 43-46 are rejected as allegedly lacking enablement. The Office Action states that

> the specification, while being enabling for one of a composition comprising 2-phenylamino-6-oxo-9-(4-hydroxybutyl)purine (HBPG) and foscarnet or acyclovir or cidofovir, does not reasonably provide enablement for the combination of any inhibitor of Herpes simplex virus thymidine kinase with any antiherpes substance comprising one or more of a pre-phosphorylated or phosphonate nucleoside analog, a pyrophosphate analog and a nucleoside analog or esters of said drugs (Office Action at page 4).

Applicant traverses this rejection for the following reason. Claims 1-3, 5, 7, 8, 10-19, 32-34, 36-40, and 43-46 cover kits and compositions comprising (a) inhibitors of Herpes simplex virus thymidine kinase ("HSV TK") selected from the group consisting of 2-phenylamino-9-substituted-6-oxopurines and 2-phenylamino-9H-6-oxopurines, or an ester, salt, or solvate thereof; and (b) an antiherpes substance that inhibits viral DNA replication comprising one or more of (1) a pre-phosphorylated or phosphonate nucleoside analog; and (2) a nucleoside analog, or any combination thereof, or an ester, salt, or solvate thereof.[1] The claimed compositions and kits are enabled, because one skilled in the art could make and use the claimed invention as of the filing date of the present application without undue experimentation. *See* MPEP 2164.01. One skilled in the art as of the priority date of the present application could have readily obtained inhibitors of Herpes simplex virus thymidine kinase and antiherpes substances that inhibit viral

[1] Claims 4, 6, 9, and 35 are cancelled.

DNA replication, as covered by the rejected claims. For example, in paragraph [0030] of the published application, applicant references Wright, U.S. Patent No. 5,646,155 ("Wright '155"), and the compound identified in the Office Action (HBPG). Wright '155 discloses many HSV TK inhibitors, along with their syntheses and characterization. For example, Table 1 of Wright '155 shows the concentration of nine compounds, the last being HBPG, at which fifty percent of either HSV1 or HSV2 TK inhibition is observed. Thus, having access to the present specification, along with Wright '155, a person of ordinary skill in the art would have been able to readily obtain the HSV TK inhibitors covered by the rejected claims at the time of filing. Furthermore, antiherpes substances that inhibit viral DNA replication are a class of compounds readily known to a person of ordinary skill in the art (*see, e.g.*, the NIAID Chemical Database referenced above). With respect to the claimed combination of the HSV TK inhibitor, and an antiherpes substance, the specification also describes how to combine these two components and how to administer them concurrently (*see, e.g.*, paragraph [0041]).

Given these considerations, applicant submits that the specification fully meets the enablement requirement of 35 U.S.C. §112, first paragraph. Reconsideration and withdrawal of this rejection is requested.

35 U.S.C. §103(a)

Claims 1-19, 32-40, and 43-46 are rejected as allegedly being unpatentable over U.S. Patent 5,646,155 ("Wright") and Naesens et al., "Recent Developments in Herpesvirus Therapy," *Herpes*, 8(1), 12-16 (2001) ("Naesens") (Office Action at page 9). In particular, the Office Action states:

> [i]t would have been obvious… to make a composition comprising a combination of an inhibitor of Herpes Simplex virus thymidine kinase and an antiherpes substance… since Wright suggests combination of oxo-guanine thymine kinase inhibitor with other antiherpes agents. Therefore, one of ordinary skill in the art would have reasonably expected that the combination… would have resulted in substantially similar or beneficial effects in the treatment of herpes infection (Office Action at pages 10-11).

Applicants respectfully disagree. Prior to the present application, inhibitors of HSV TK were believed to *antagonize* the activity of antiherpes nucleoside analogs that inhibit viral DNA

replication, such as acyclovir and ganciclovir. Applicants have identified numerous examples of prior art studies documenting the antagonism of antiherpes nucleoside analogs by various inhibitors of HSV TK. For example, Ashton *et al.* reported in 1989[2] that the HSV TK inhibitor 9-[[(Z)-2-(hydroxymethyl)cyclohexyl]methyl]guanine antagonized the activity of ganciclovir in a HSV-1 infected cell culture and worsened the condition of HSV-1 infected mice:

> [i]n MRC-5 cell culture, [9-[[(Z)-2-(hydroxymethyl)-cyclohexyl]methyl]guanine] failed to inhibit the replication of HSV-1 at the highest concentration tested (100 microgram/mL). However, **the protection of MRC-5 cells against HSV-1 challenge by the TK-dependent agent ganciclovir** (at 0.62 microgram/ml) **was completely abolished** by [9-[[(Z)-2-(hydroxymethyl)-cyclohexyl]methyl]guanine] **at 6.2-12.5 micrograms/ml and above**… **Surprisingly, mice inoculated orofacially with HSV-1** and treated with [9-[[(Z)-2-(hydroxymethyl)-cyclohexyl]-methyl]guanine] (170 or 500 micrograms/ml in drinking water) **rapidly developed lesions** which were significantly more severe than those of the control animals.[3]

Thus, the prior art discloses to one skilled in the art that a combination of a HSV TK inhibitor with an antiherpes nucleoside analog such as ganciclovir would reduce or eliminate the therapeutic effect of the antiherpes nucleoside analog.

Similarly, Klein *et al.*, in 1990, reported the *in vivo* antagonism of the antiherpes nucleoside analog acyclovir ("ACV") by co-administration of the HSV TK inhibitor (±)-9-[[(Z)-2-(hydroxymethyl)cyclohexyl]methyl]guanine ("L-653,180") when treating HSV-1-induced skin infection:

> [t]he evolution of skin lesions in ACV treated mice was dose dependent starting with a dose of 4.2 mg/kg (no differences were seen between a dose of 1.4 and 4.2 mg/kg). A dose of 14.5 mg/kg reduced slightly the intensity of lesions and a dose of 46 mg/kg suppressed the development of lesions almost completely… **When L-653,180 was added to the antiviral treatment the suppressive effect of ACV was reversed** and severe lesions were observed in

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[2] Ashton, W.T.; Meurer, L.C.; Tolman, R.L.; Karkas, J.D.; Liou, R.; Perry, H.C.; Czelusniak,S.M.; Klein, R.J., "A potent, selective, non-substrate inhibitor of HSV-1 thymidine kinase: (±)-9-[[(Z)-2-(hydroxymethyl)cyclohexyl]methyl]guanine and related compounds," Meeting Abstract, *Nucleos. Nucleot.* 8, 1157-1158 (1989) (Copy attached in accompanying Information Disclosure Statement)

[3] *Id.* at page 1158, emphasis added

> mice treated with doses up to 14.5 mg/kg of ACV. Only a dose of 46 mg/kg of ACV was able to prevent to a significant extent the enhancing effect of the TK inhibitor.[4]

Accordingly, one skilled in the art would have understood, based on Klein, that administering an HSV TK inhibitor would negate the therapeutic effect of doses of acyclovir against HSV-1 below 46 mg/kg, while acyclovir could be therapeutically effective at lower doses (e.g., 4.2 mg/kg) against HSV-1 in the absence of a HSV TK inhibitor.

Together, these prior art publications demonstrate that one skilled in the art would have understood inhibitors of HSV TK inhibitors to *antagonize* the antiherpes effect of nucleoside analogs that inhibit viral DNA replication, such as acyclovir and ganciclovir. Accordingly, it would not have been obvious to one skilled in the art to combine an inhibitor of HSV TK and an antiherpes nucleoside analog that inhibits viral DNA replication, and they would certainly not have expected that such a combination "would have resulted in substantially similar or beneficial effects in the treatment of herpes infection," as alleged in the Office Action (Office Action at page 11). In contrast, applicant has surprisingly discovered combinations of an inhibitor of HSV TK and an antiherpes compound that inhibits viral DNA replication, where the combinations have unexpected activity against HSV during *in vivo* studies (*See, e.g.,* paragraphs [0007] and [0043]-[0055] of the present application, published as US2004/0259832).

As amended, the rejected claims cover kits and compositions comprising (a) inhibitors of Herpes simplex virus thymidine kinase selected from the group consisting of 2-phenylamino-9-substituted-6-oxopurines and 2-phenylamino-9H-6-oxopurines, or an ester, salt, or solvate thereof, in a first dose less than a median therapeutically effective dose of the inhibitor of Herpes simplex virus thymidine kinase; and (b) an antiherpes substance that inhibits viral DNA replication comprising one or more of (1) a pre-phosphorylated or phosphonate nucleoside analog; and (2) a nucleoside analog, or any combination thereof, or an ester, salt, or solvate thereof, in a second dose less than a median therapeutically effective dose of the antiherpes substance; where the first dose and the second dose together form a therapeutically effective dose of the combination.

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[4] Klein, R.J.; Czelusniak, S.M., "Effect of a thymidine kinase inhibitor (L-653,180) on antiviral treatment of experimental herpes simplex virus infection in mice," *Antiviral Res.* 14, 207-214, 210 (1990), emphasis added ("Klein") (Copy attached in accompanying Information Disclosure Statement)

Wright does not disclose or render obvious such compositions and kits. Instead, Wright discloses certain 9-substituted-N^2-phenylguanine compounds, such as HBPG (*See, e.g.,* Wright at col. 6, line 5 – col. 8, line 5 and Example 3, col. 13). Wright further discloses that these compounds "can be used as the sole active agents, or can be used in combination with other ingredients, e.g., direct antiviral drugs…" (Wright, col. 9, lines 59-61). Wright not only fails to "expressly disclose any particular combination of an inhibitor of Herpes simplex virus thymidine kinase and another antiherpes substance," as noted at page 10 of the Office Action, but Wright also fails to disclose or render obvious the combination of a HSV TK inhibitor with an antiherpes substance as claimed. Wright does not mention, let alone call into question, prior art studies showing that inhibitors of HSV TK were known to antagonize the antiherpes effect of nucleoside analogs that inhibit viral DNA replication, as discussed above. Accordingly, Wright does not disclose or render obvious the claimed compositions and kits.

The Office Action also takes the position that one skilled in the art would have combined an oxo-guanine thymine kinase inhibitor with antiherpes agents based on Wright in combination with Naesens (Office Action at page 10). Applicants respectfully disagree. First, one skilled in the art would not have combined Naesens with Wright. Wright specifically recites the combination of the 9-substituted-N^2-phenylguanine compounds with "direct antiviral drugs," (Wright at col. 9, line 61), while Naesens describes antiherpes compounds that undergo "specific activation by herpes virus-encoded kinases, that convert these nucleoside analogues to their monophosphate metabolites" (Naesens at page 12). Thus, Wright recites combination with "direct" acting antiviral drugs (Wright at col. 9, line 61), while Naesens refers to compounds that undergo "specific activation" (Naesens at page 12). Second, Naesens does not address, let alone refute, prior art studies showing that inhibitors of HSV TK were known to antagonize the antiherpes effect of nucleoside analogs that inhibit viral DNA replication, as discussed above. For at least these reasons, Naesens does not cure the deficiencies of Wright.

Furthermore, it is well established that "[i]n order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989). Here, none of the references relied upon by the Examiner, taken alone or in combination, disclose or render obvious compositions and kits that include the

claimed combination of an inhibitor of HSV TK and an antiherpes nucleoside analog. The Examiner has not provided any basis for one skilled in the art to have modified the disclosure of Wright to produce the claimed compositions or kits, especially in light of prior art references (described above) disclosing combinations of various inhibitors of HSV TK and antiherpes nucleoside analogs where the HSV TK inhibitor was actually reported to *antagonize* the *in vitro* activity of the antiherpes nucleoside analog. Accordingly, Applicants request reconsideration and withdrawal of the rejection of these claims.

CONCLUSION

Applicant submits that all claims are in condition for allowance, and respectfully request a Notice of Allowance. Applicant received a Notice of Panel Decision from Pre-Appeal Brief Review dated October 14, 2008, indicating that "[t]he time period for filing an appeal brief will be reset to be one month from mailing this decision, or the balance of the two-month time period running from the receipt of the notice of appeal, whichever is greater." Applicant files this Amendment in Reply to Office Action of March 12, 2008 with the enclosed Petition for Three-Month Extension of Time, Request for Continued Examination (RCE) and Information Disclosure Statement (IDS) on the first business day after the (Monday) February 16, 2009 Federal Holiday.

All fees are being paid concurrently herewith, including the Three-Month Petition for Extension of Time Fee on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket Number 07917-0183001.

Respectfully submitted,

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